REMARKS

The Applicant has thoroughly reviewed the outstanding Office Action including the Examiner's remarks and the references cited therein. The following remarks are believed to be fully responsive to the Office Action, and when coupled with the above amendments, are believe to render all the claims at issue patentably distinguishable over the cited references. With this Amendment. claims 7 and 15 are canceled and claims 3, 5, 6, 8, 9, 11, 13 and 14 are amended. Accordingly, claims 1-6, 8-14 and 16-19 are now pending in this application.

Claim Rejections – 35 U.S.C. § 112

The Examiner has rejected claims 3, 6-7, 11 and 14-15 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. With this Amendment, claims 7 and 15 are canceled without prejudice, and claims 3, 5, 6, 8, 9, 11, 13 and 14 are amended in a manner responsive to the Examiner's concerns. Accordingly, Applicant respectfully submits that the Section 112 rejection has been overcome.

Claim Rejections - 35 U.S.C. § 102

The Examiner rejected claims 1-3 and 6 under 35 U.S.C 102(b) as being anticipated by Bodor *et al.*, (Acta Pharma Nord. 1989, 1(4), 185-193). Applicant respectfully traverses this rejection as applied to claims 1-3 and 6 and asserts that the §102 prior art rejection is defective and the Bodor *et al.* reference does not anticipate claims 1-3 and 6 of this application.

A prior art reference anticipates a claim only if the reference discloses expressly or inherently all the elements and limitations of the claim (*Kalman v. Kimberely-Clark*, 713 F.2d 760, 771, 218 USPQ 781 (Fed. Cir. 1983)). If even one element or limitation of the claim is missing, a §102 rejection fails, as 35 U.S.C §103 makes clear in its subsection:

"[A] patent may not be obtained thought the invention *is not identically disclosed or described* as set forth in section 102 in this title, if ....."

The Examiner relied on page 186, first and second paragraph of Bodor *et al*, asserting that the composition of Bodor *et al.* is prepared in a manner similar to the method described in Example 5 at page 13 of this instant specification application. The Applicant would like to point out that Example 5 at page 13 of this instant specification is actually a comparative example of this application, which means it is an example the inventors prepared by using prior art technology (the niosome thus made comprised free estriol and Span 60 (a surfactant)), as a comparison with the actual working example 6 of this invention (the niosome thus made comprised of a cyclodextrin complex of estriol, and a vesicle formed by Span 60). In other words, Example 5 is not the instant invention (Example 6 is), and the Examiner is erred on relying on prior art teachings to reject the comparative example, instead of the working example this application claims. Bodor *et al.* teach the effects of 2-hydroxypropyl-ß-cyclodextrin (2-HPCD) on the solubility characteristics of several drugs in water and on the transdermal delivery of 17ß-estradiol by adding drugs to aqueous solution containing various amounts of 2-HPCD and sonicating the mixture for an hour, then allowed the mixed solution to equilibrate in the dark for 48 hrs before diluting it with 50% methanol. The prepared aqueous 2-HPCD solution containing drugs were then used in skin permeation studies (See "Abstract" and "Solubility studies" of Bodor *et al.*). However, Bodor *et al* do not teach the presently claimed invention, particularly, they do not teach a composition of claim 1, which comprises a niosome that retained in its structure: (1) a cyclodextrin inclusion complex formed by a cyclodextrin compound and a steroidal active agent; and (2) a vehicle formed by a nonionic surfactant. In other words, Bodor *et al.* do not identically disclose or describe this invention, and the §102 prior art rejection is defective.

Moreover, Bodor *et al.* do not make it obvious to do so either. As explained above, Bodor *et al.* only teach forming an inclusion cyclodextrin complex of drugs including

17ß-estradiol, they do not teach or suggest forming a cyclodextrin inclusion complex of estriol first, then combining the inclusion complex with a vesicle formed by non-ionic surfactant, and thereby obtaining a niosome (Example 6 of this application) that facilitates the transdermal delivery of estriol at least 2-7 fold (*See* Fig 3 of this invention) compared with the niosome containing free estriol (*See* Example 5 of this application). Therefore, a person skilled in the art would not have conceived the idea of forming a drug inclusion complex first, then combining it with a vesicle formed by non-ionic surfactant, to obtain the niosome of this invention in view of the teachings of Bodor *et al.* In light of the recitations of claims 1-3 and 6, as amended, applicant respectfully requests the rejection of claims 1-3 and 6 of this application as being anticipated by Bodor *et al* be withdrawn.

The Examiner furthered rejected claim 19 under 35 U.S.C 102(b) as being anticipated by Bodor *et al.*, (Acta Pharma Nord. 1989, 1(4), 185-193). Applicant respectfully traverses this rejection as applied to claim 19 and asserts that the §102 prior art rejection is defective and the Bodor *et al.* reference does not anticipate claim 19 of this application.

Claim 19 of this instant invention is directed to a method for facilitating transdermal delivery of a steroidal active agent, comprising the step of administering to a human or an animal the composition of claim 1. As explained above, Bodor *et al.* do not teach or suggest the composition of claim 1, nor do they teach or suggest the use of the novel composition of claim 1 of this invention. In other words, Bodor *et al.* do not identically disclose claim 19, nor would a person skilled in the art be capable of conceiving the idea of claim 19 of this invention in view of Bodor *et al.* In light of the recitations of claim 19, applicant respectfully requests the rejection of claim 19 of this application as being anticipated by Bodor *et al.* be withdrawn.

Claim Rejections - 35 U.S.C. § 103

The Examiner rejected claims 4-5 and 7-8 under 35 U.S.C. 103(a) as being unpatentable over Bodor *et al.*, (Acta Pharma Nord. 1989, 1(4), 185-193) in view of Siguroardottir *et al.* (Drug Development and Industrial Pharmacy, 1994, 20(9), 1699-1078). Applicant respectfully traverses this rejection as applied to claims 4-5 and 7-8 on the basis that the art cited by the Examiner, either alone or in combination, fails to teach or suggest the claimed invention.

The differences between the teachings of Bodor *et al.* and that of this instant invention have been fully explained as above. As to Siguroardottir *et al.*, the Examiner relied on their description at page 1702, first paragraph in rejecting claims 4-5 and 7-8 of this application, contended that a composition comprising other nonionic surfactants like glyceryl monosterate, *etc.* was obtained. This is not true. A careful review of the related description provided in "Materials and Methods" of Siguroardottir *et al.* reveals that the purpose of Siguroardottir *et al.*'s study was to investigate the effect of HPβCD on the release of drugs from topical vehicle system, where hydrocortisone was used as a sample drug and 3 vehicle systems were investigated[1], including the oil-in-water cream system the Examiner identified. The third vehicle system, particularly "HPβCD containing oil-in-water (o/w) creams consisting of 0.5~3.5% hydrocortisone", in which the oily cream consisted of 0.25% polysorbate 80, 1.25% cetostearyl alcohol, 1.25% liquid paraffin, 1.5% glyceryl monosterate 40-50, 4% glycerol, and 7% sorbitol was mixed with 0~10% HPβCD to form an oil-in-water system, instead of a niosome as this application claims. The HPβCD mixed with the Uniderm® 1% cream vehicle system was prepared by mixing all ingredients and heating the solution or suspension in an autoclave to 120°C for 20 min, followed by equilibrating at room temperature for at least 3 days

1 The 3 vehicle systems were: "1) Aqueous HPβCD solution consisting of 1% hydrocortisone in aqueous HPβCD MS 0.6 solutions; 2) A hydrogel consisting of 1% hydrocortisone, 0.6% HPβCD MS 0.6, and 3.5% sodium carboxymethyl cellulose in water; and 3) HPβCD containing oil-in-water (o/w) creams consisting of 0.5~3.5% hydrocortisone." *See* page 1701, last paragraph of Siguroardottir *et al.*

before conducting a permeation test across hairless mouse skin. Siguroardottir *et al* found that in aqueous vehicle systems, hydrophilic cyclodextrin like HPβCD can promote dermal and transdermal delivery of lipophilic water-insoluble drugs with result comparable to that obtained from Uniderm®.

No where in Siguroardottir *et al.*'s disclosure did they teach or suggest forming a niosome retaining in its structure: (1) a cyclodextrin inclusion complex formed by a cyclodextrin compound and a steroidal active agent in a molar ratio of 10 to 1; and (2) a vehicle formed by a nonionic surfactant, in which the nonionic surfactant vesicle and the cyclodextrin inclusion complex is mixed in a ratio of 25 to 1. Therefore, neither Bodor *et al.* nor Siguroardottir *et al.* (nor the combination of the two) had taught or suggested this invention. Applicant respectfully submits that claims 4-5 and 7-8 are patentable over Bodor *et al* (Acta Pharma Nord. 1989, 1(4), 185-193) in view of Siguroardottir *et al* (Drug Development and Industrial Pharmacy, 1994, 20(9), 1699-1078).

The Examiner further rejected claims 9-18 under 35 U.S.C. 103(a) as being unpatentable over Bodor *et al.*, (Acta Pharma Nord. 1989, 1(4), 185-193) in view of Loftsson (US 5,472,954). Applicant respectfully traverses this rejection as applied to claims 9-18 on the basis that the art cited by the Examiner, either alone or in combination, fails to teach or suggest the claimed invention.

The differences between the teachings of Bodor *et al.* and that of this instant invention have been fully explained as above. As to Loftsson, he teaches a method of enhancing the complexation of cyclodextrin with a lipophilic and/or water-liable active ingredient, comprises mixing 1) cyclodextrin, 2) a pharmacologically inactive water-soluble polymer such as cellulose derivatives, polysaccharides or polypeptides, and 3) said water-liable active ingredient such as steroid in an aqueous medium, in which the polymer and cyclodextrin being dissolved in the aqueous medium before the active ingredient is added. However, nowhere in Loftsson did he teach or suggest this invention. Hence, it is clear neither Bodor *et*

al. nor Loftsson had taught or suggested this invention, that is, forming a niosome retained in its structure: (1) a cyclodextrin inclusion complex formed by a cyclodextrin compound and a steroidal active agent in a molar ratio of 10 to 1; and (2) a vehicle formed by a nonionic surfactant, in which the nonionic surfactant vesicle and the cyclodextrin inclusion complex is mixed in a ratio of 25 to 1. Therefore, Applicant respectfully submits that claims 9-18 are patentable over Bodor *et al.* (Acta Pharma Nord. 1989, 1(4), 185-193) in view of Loftsson (US 5,472,954).

CONCLUSION

In view of the foregoing amendments and remarks, Applicant believes that all the claims as amended herein are distinguishable from the cited prior art, and the Examiner is respectfully requested to enter the requested amendments and to pass this application for allowance.

Respectfully submitted,

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Date: 6/22/07

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